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Tea tree oil formulations

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ABSTRACT

A formulation containing 0.25%-15.0% w/v tea tree oil and 1-15% w/v of a surfactant. The formulation may be used as a mouthwash, cream, shampoo or anti-dandruff preparation.

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Regulation 3.2

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ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Invention Title: "TEA TREE OIL FORMULATIONS"

The following statement is a full description of this invention, including the best method of performing it known to me/us:

above drugs, which are taken orally, is of potential adverse effects as well as cost considerations which apply to the newer systemic antifungal drugs. It is also known that some drugs have limited areas of application. For example, in the case of griseofulvin, this drug is active against dermatophytes, but has no effect against yeasts or other fungi.

It is also reported in the Nenoff et all article *supra* that tea tree oil also has therapeutic activity against several bacterial infections inclusive of *Staphylococcus aureus, E coli* and *Propionibacterium acnes*.

Reference also may be made to Concha et al, Journal of the American Podiatric Medical Association **88**; 10; 489-492 (1998) which states that tea tree oil is receiving much attention as a natural remedy for bacterial and fungal infections of the skin and mucosa as discussed above. Concha et al also advises that tea tree oil has therapeutic activity against bacterial infections caused by *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*. Carson et al, J. Antimicrob. Chemother. **35** 421- (1996) states that tea tree oil has a wide spectrum of antimicrobial activity and is relatively non toxic when applied topically.

In Bassett et al, Med. J. Aust. **153** 455 (1990) tea tree oil was reported to have a significant effect in ameliorating acne with fewer side effects in comparison with benzoyl peroxide. Concha et al

supra advises that tea tree oil appears to be effective in treatment of tinea pedis, bromhidrosis and other inflammatory foot problems. Other clinical investigations have been conducted on the use of tea tree oil for onchomycosis, furunculosis, trichomonal vaginitis and oral gingivitis.

However, tea tree oil has received a lot of attention in relation to treatment of diseases caused by *M. furfur* discussed above and in particular seborrhoeic dermatitis and severe dandruff. Hammer et al, Antimicrob. Agents Chemother. **44**; 2; 467-469 (2000) reports that tea tree oil may be a suitable alternative topical agent for *Malassezia* infections to ketoconazole which was found to be more active than other drugs micronazole and econazole in treatment of Malassezia infections. This reference supports the view that many patients may prefer the use of tea tree oil as a natural remedy when used topically as opposed to clinical drugs such as ketoconazole. A similar finding was made in Hammer et al, Journal of Medical and Veterinary Mycology **35** 375-377 (1997) which stated that although skin conditions involving *M. furfur* can be treated topically with agents such as zinc pyrithione, selenium sulphide and coal tar, or systemically with ketoconazole, itaconazole or fluconazole, the use of tea tree oil as a topical agent may be used where other treatments have failed, where prophylaxis is required or simply as an alternative therapy.

invention may also include other topical active components which include zinc pyrithione, sulphur, selenium sulphide, coal tar, salicylic acid and piroctone olamine. These additional components may be present in a concentration of 0.1-2.0% w/v.

It also will be appreciated that the formulation of the invention may be utilised for any therapeutic effect known in the art which may be achieved by tea tree oil such as the abovementioned anti-fungal or antibacterial applications. The formulation of the invention may also be used as a mouthwash, cream, shampoo or any other suitable topical usage. The formulation of the invention may also be used for veterinary purposes such as a pet shampoo as well as for application to humans.

Surfactants useful as shampoos are described in "HARRY'S COSMETICOLOGY" Seventh Edition (1982) Chemical Publishing Company of the USA which publication is totally incorporated herein by reference. The surfactants useful for inclusion in shampoos may include principal surfactants to provide detergency and foam and auxiliary surfactants to provide detergency, foam, and hair condition. Principal surfactants may comprise non-ionic surfactants or cationic surfactants, but it is usually preferred to use anionic surfactants because of their superior foaming properties and lower cost. Such anionic surfactants may include soaps i.e. metallic or alkanolamine salts of fatty acids, alkyl benzene sulfonates, C_{14-16}

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TITLE

"TEA TREE OIL FORMULATIONS"

THIS INVENTION relates to improving the treatment efficiency of tea tree oil when used as a therapeutic agent.

Tea tree oil when used as a therapeutic agent has antifungal activity as reported in Nenoff et al, Skin Pharmacol 9 388-394 (1996). In this reference tea tree oil was found to inhibit growth of clinical fungal isolates including *Candida* sp including *Candida albicans* which causes candidiasis of skin, mucous membranes and nails, *Malassezia furfur* which causes pityriasis versicolor, follicular pityriasis, seborrhoeic dermatitis and pityriasis capitis (i.e. severe dandruff) and *Trichosporon rubrum, Trichosporon mentagrophytes* and *Microsporum canis,* which cause ringworm or tinea of scalp, skin (in particular glabrous or hairless skin) and nails. As discussed in Ellis and Watson, Aust. Prescr. 19; 3; 72-74 (1996) these infections can be considered to be broadly classified as cutaneous fungal infections. Such infections are usually treated topically, but nail and hair infections, widespread dermatophytosis and chronic non responsive yeast infections are best treated with oral antifungal drugs which are conventional drugs including griseofulvin, ketoconazole, fluconazole, itraconazole and terbinafine.

However, as stated in the Ellis and Watson reference, the major disadvantage of the use of systemic therapy using the

above drugs, which are taken orally, is of potential adverse effects as well as cost considerations which apply to the newer systemic antifungal drugs. It is also known that some drugs have limited areas of application. For example, in the case of griseofulvin, this drug is active against dermatophytes, but has no effect against yeasts or other fungi.

It is also reported in the Nenoff et all article *supra* that tea tree oil also has therapeutic activity against several bacterial infections inclusive of *Staphylococcus aureus, E coli* and *Propionibacterium acnes*.

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supra advises that tea tree oil appears to be effective in treatment of tinea pedis, bromhidrosis and other inflammatory foot problems. Other clinical investigations have been conducted on the use of tea tree oil for onchomycosis, furunculosis, trichomonal vaginitis and oral gingivitis.

However, tea tree oil has received a lot of attention in relation to treatment of diseases caused by *M. furfur* discussed above and in particular seborrhoeic dermatitis and severe dandruff. Hammer et al, Antimicrob. Agents Chemother. **44**; 2; 467-469 (2000) reports that tea tree oil may be a suitable alternative topical agent for *Malassezia* infections to ketoconazole which was found to be more active than other drugs micronazole and econazole in treatment of Malassezia infections. This reference supports the view that many patients may prefer the use of tea tree oil as a natural remedy when used topically as opposed to clinical drugs such as ketoconazole. A similar finding was made in Hammer et al, Journal of Medical and Veterinary Mycology **35** 375-377 (1997) which stated that although skin conditions involving *M. furfur* can be treated topically with agents such as zinc pyrithione, selenium sulphide and coal tar, or systemically with ketoconazole, itaconazole or fluconazole, the use of tea tree oil as a topical agent may be used where other treatments have failed, where prophylaxis is required or simply as an alternative therapy.

A major infection of commercial significance as described above which is caused by *M. furfur* is seborrhoeic dermatitis and dandruff (otherwise called pityriasis capitis) which is seborrhoeic dermatitis of the scalp. Dandruff itself is not a disease, but may be symptomatic of hair loss and even baldness. Dandruff can also be embarrassing, leading to fine particles or "snowflakes" appearing on clothes, especially in the shoulder region. The usual symptoms of dandruff include a dry, flaky scalp or itchy waxy scales that stick to the hair, which may cause severe irritation. Dry dandruff usually indicates insufficient brushing of the hair or poor circulation of blood to the scalp. Waxy dandruff may result from overactive sebaceous glands. Severe dandruff may indicate psoriasis.

Conventional shampoos that have been used to control or reduce dandruff, which include anti-dandruff agents such as selenium sulfide, zinc pyrithione or coal tar are deficient because such anti-dandruff agents are toxic if used in excess and can cause scalp irritation. One solution to these problems is to reduce the amount of anti-dandruff agent but this may lead to decreased effectiveness in use.

Tea tree oil has also been used in shampoos in relatively dilute concentrations which may be from 0.5-2.0%. Tea tree oil possess at least 48 organic compounds, having both antiseptic and antifungal properties and has therefore been incorporated in products

for treatment of a variety of skin disorders, including dandruff. Such shampoos have been described as having anti-dandruff properties but this is speculative and unsupported by efficacy data.

These conventional tea tree shampoos also have a percentage of surfactant solids in the formulation of 20-50% w/v. These tea tree oil shampoos are sold in Australia under the THURSDAY PLANTATION trade mark. Tea tree oil as stated above is considered to be advantageous when compared to the conventional treatments described above because it is a natural product and therefore considered to be non toxic. Tea tree oil as stated above has also been shown to be useful in treatment of other yeast and fungal infections such as tinea pedis and in this regard has a minimum inhibitory concentration of 0.25% v/v as reported in Tong et al Aust. J. Dermatol (1992) 33 145-9.

DE 19800982 refers to an ointment for treatment of dandruff, which comprises a mixture of essential oils, inclusive of evening primrose oil, tea tree oil, lavender oil, cod liver oil, borage oil, jojoba oil, nutmeg oil and D-panthenol in a lanolin base. However, this ointment is relatively expensive and is not intended for use as a shampoo.

DI29913476 refers to a composition for treating skin disorders inclusive of dandruff containing tea tree oil, bay-tree oil, peppermint oil and isopropanol and is also not intended for use as a

shampoo.

US5750108 refers to a hair treatment system and kit for invigorating hair growth, which involves use of a first treatment comprising tea tree oil and a second treatment comprising chlorine dioxide. This method is relatively complicated and is not intended for use as a shampoo.

One problem, which has been ascertained by the present inventors, that is associated with the use of tea tree oil therapeutic products such as anti-dandruff shampoos, is that the level of surfactant in such shampoos may adversely effect the active or non-bound level of tea tree oil in the shampoo. If the level or surfactant is excessive, then it may bind the tea tree oil in a surfactant matrix which will mean that there is insufficient concentration of free or non-bound levels of tea tree oil to be effective in use. In this regard it will be appreciated that when tea tree oil shampoos or other products containing tea tree oil are being formulated that a level of surfactant is included to allow for emulsification of the tea tree oil and also to retain relevant foaming and/or cleansing characteristics which are satisfactory to the consumer.

It is therefore an object of the invention to provide a therapeutic formulation containing tea tree oil which alleviates the problem described above.

The formulation of the invention comprises a

concentration of tea tree oil of 0.25-15% w/v and a total surfactant concentration of 1-15% w/v.

It has now been found, in accordance with the invention, that if the surfactant concentration is maintained between 1-15% w/v, for therapeutic products having a tea tree oil concentration of 0.25-15% w/v, then significant amounts of the tea tree oil present in the formulation is in free or non bound form i.e. it is not bound to the surfactant and thus is in an "active" concentration.

The invention also provides a method of increasing the efficiency of action of use of tea tree oil as a therapeutic which includes the step of providing a formulation which provides a maximum concentration of unbound or free tea tree oil in a surfactant wherein the level of surfactant is maintained at a maximum concentration of 15% w/v.

The term "tea tree oil" as used herein includes not only tea tree oil *per se* i.e. in its natural form as well as one or more active components thereof e.g. terpinen-4-ol and/or alpha terpineol. The term "tea tree oil" as used herein refers to natural forms of tea tree oil which are obtained from any appropriate *Melaleuca* species or *Leptospermum* species such as, for example, *M.alternifolia, M.linariifolia* and *M.dessitafolia*, as well as modified extracts containing the aforementioned active components *per se*.

It also will be appreciated that the composition of the

invention may also include other topical active components which include zinc pyrithione, sulphur, selenium sulphide, coal tar, salicylic acid and piroctone olamine. These additional components may be present in a concentration of 0.1-2.0% w/v.

It also will be appreciated that the formulation of the invention may be utilised for any therapeutic effect known in the art which may be achieved by tea tree oil such as the abovementioned anti-fungal or antibacterial applications. The formulation of the invention may also be used as a mouthwash, cream, shampoo or any other suitable topical usage. The formulation of the invention may also be used for veterinary purposes such as a pet shampoo as well as for application to humans.

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alpha olefin sulfonates, or alkyl sulfates especially those derived from lauryl and myristyl alcohols. Lauryl sulfates give a greater volume of lather and myristyl sulfates greater richness. The most popular anionic surfactants are sodium lauryl sulfate, sodium lauryl ether sulfate or ammonium lauryl sulfate. Use also may be made of alkyl polyethylene glycol sulfates or alkyl ether sulfates sulfosuccinates, monoglyceride sulfates, fatty glyceryl ether sulfonates, isethionates, methyl laurides, acyl sarcosinates, acyl peptides, acyl lactylates or polyalkoxylated ether glycollates.

Nonionic surfactants are usually used as additives to anionic surfactants and may include C_{12-18} monoethanolamides or isopropanolamides which are used in conjunction with lauryl sulfates on a basis of 1-15 parts per 100 parts of anionic surfactant. Diethanolamides may also be used as well as polyalkoxylated derivatives including ethoxylated fatty alcohols, ethoxylated alkyl phenols, ethoxylated fatty amines and fatty acid amides, poloxamers, sorbitol esters, polyglyceryl ethers or amine oxides.

Amphoteric surfactants also are generally used as auxiliary surfactants inclusive of (1) long chain substituted amino acids such as sodium cocaminopropionate, or derivatives and (2) long chain betaines inclusive of amidobetaines or long chain imidazoline derivatives.

Particularly preferred principal surfactants are ammonium

lauryl sulfate, sodium ether lauryl sulfate and triethanolamine lauryl sulfate. Particularly preferred auxiliary surfactants are cocamide DEA and cocoamidopropyl betaine. These surfactants when mixed together compliment each other in terms of cleansing, foaming, thickening and emulsification.

EXPERIMENTAL

EXAMPLE 1

This was a randomised, single blind, parallel group study investigating the efficiency and tolerability of tea tree oil in concentrations of 1%, 2.5% and 5.0%, 1% zinc pyrithione and placebo in patients with mild to moderate dandruff. The 1% zinc pyrithone formulation was a conventional dandruff shampoo marketed under the ZP11 trade mark. Relevant formulations containing tea tree oil were as follows:

(a) 1.0% tea tree oil formulation

Tea Tree (Melaleuca Alternifolia) Oil	1.00%
PEG-35 Castor Oil (surfactant)	2.00%
Antioxidant	0.20%
Fragrance	0.50%
Sodium Laureth Sulfate (surfactant)	14.00%
Cocoamidopropyl Betaine (surfactant)	4.50%
Thickener	0.80%
Pearling Agent	3.00%
Preservative	0.50%
Purified Water	73.50%
	100.00%

(b) 2.5% tea tree oil formulation

Tea Tree (Melaleuca Alternifolia) Oil	2.50%
PEG-35 Castor Oil (surfactant)	5.00%
Antioxident	0.20%
Fragrance	0.50%
Sodium Laureth Sulfate (surfactant)	14.00%
Cocoamidopropyl Betaine (surfactant)	4.50%
Thickener	1.70%
Pearling agent	3.00%
Preservative	0.50%
Purified Water	68.10%
	100.00%

(c) 5.0% tea tree oil formulation

Tea Tree (Melaleuca Alternifolia) Oil	5.00%
PEG-35 Castor Oil (surfactant)	10.00%
Antioxidant	0.20%
Fragrance	0.50%
Sodium Laureth Sulfate (surfactant)	14.00%
Cocoamidopropyl Betaine (surfactant)	4.50%
Thickener	1.90%
Pearling agent	3.00%
Preservative	0.50%
Purified Water	60.40%
	100.00%

Demography

One hundred and fifty eight subjects were enrolled in the study and randomised to receive one of five possible study medications as described above. Thirty-two subjects were randomised to each of the 1% Tea Tree Oil, 1% zinc pyrithione and placebo groups and thirty-one subjects to each of the 2.5% Tea Tree Oil and 5% Tea Tree Oil groups.

The age of the subjects ranged from 15 to 77 years (with a mean age 32 years). Ninety-three (59%) subjects were male and the vast majority (107 subjects, 68%) where classified as white (caucasian).

Efficacy

The efficacy measures were based on the precent change, from baseline (ie Week 0), in the whole Scalp Score as well as the three components of the Patient Self Assessment. Percent change was calculated as follows:

$$\text{Percent change} = \frac{\text{Visit Value - Baseline Value}}{\text{Baseline Value}} \times 100$$

Whole Scalp Score

Lesions were examined and scored on a quadrant-area-severity scale. The scalp was divided into four quadrants. The area of involvement of each quadrant will be measured on a 1-5 scale where:

1 = less than 10% involvement,

2 =10-30% involvement,

3 = 30-50% involvement,

4 = 50-70% involvement and

5 = more than 70% involvement.

The total area of involvement was obtained by adding the four quadrant scores.

Severity was measured by a 0-3 scale where:

0 = indicates healed

1 = mild

2 = moderate

3 = severe.

The total severity score will be obtained by adding the four quadrant scores.

The whole scalp lesion score will then be obtained by multiplying the total area of involvement by the total severity score.

RESULTS

It was found that the percent change values exhibit relatively high variability and also that the values are not symmetrically distributed (since the mean and median values are often substantially different). For this reason the analysis included both parametric and non-parametric methods. The largest percent decrease in the Whole Scalp Score was exhibited by subjects receiving 1% zinc pyrithione (a median percent reduction of 43%) and the smallest percent decrease was exhibited by subjects receiving 2.5% Tea Tree Oil (a median percent reduction of 8.2%). After making adjustments for multiple testing, there were no statistically significant differences between the treatment groups with respect to percent change from baseline to Week 4 in the Whole Scalp Score.

Patient Self Assessment

Patients were requested to make a self-assessment at each visit for the following parameters: skin scalp scaling, itching and greasiness on a 100 mm visual analogue scale, with the two

extremes being "none" and "worst ever".

Scaling

It was found that the largest percent decrease in the Scaling Score was exhibited by subjects receiving 1% zinc pyrithione (a median percent reduction of 48%) and the smallest percent decrease was exhibited by subjects receiving placebo (a median percent reduction of 20.2%). After making adjustments for multiple testing, there were no statistically significant differences between the treatment groups with respect to percent change from baseline to Week 4 in the Scaling Score.

Itching

It was found that the largest percent decrease in the Itching Score was exhibited by subjects receiving 5% tea tree oil (a median percent reduction of 54%) and the smallest percent decrease was exhibited by subjects receiving placebo (a median percent reduction of 20%). After making adjustments for multiple testing, there were no statistically significant differences between the treatment groups with respect to percent change from baseline to Week 4 in the Itching Score.

Greasiness

It was found that the largest percent decrease in the Greasiness Score was exhibited by subjects receiving placebo (a median percent reduction of 48%) and the smallest percent decrease

was exhibited by subjects receiving 1% tea tree oil (a median percent reduction of 26.8%). After making adjustments for multiple testing, there were no statistically significant differences between the treatment groups with respect to percent change from baseline to Week 4 in the Greasiness Score.

EXAMPLE 2

126 male or female patients aged 14 or older were recruited to a randomised, single blind, parallel group study with the objective of investigating the efficacy and tolerability of 5% tea tree oil (TTO) and placebo, in patients with mild to moderate dandruff.

At the initial study visit patients underwent a medical examination, and patients who satisfied the study eligibility criteria and consented to participate were randomised to daily applications of either 5% tea tree oil or placebo, over a four-week period. Patients were assessed after two and four weeks of study medication. At each visit, including the initial study visit, the lesions were examined and scored on a quadrant-area severity scale. In addition, patients were required to record their own assessment of skin scaling, itching and greasiness on a visual analogue scale.

A total of 126 patients were enrolled in the study with 63 patients randomised to each medication. The 5% tea tree oil formulation comprised the following:

Tea Tree (Melaleuca Alternifolia) Oil	5.00%
Cocamide DEA (surfactant)	8.00%
Ammonium Lauryl Sulfate (surfactant)	5.40%
Pearling agent	0.50%
Purified Water	81.10%
	100.00%

The primary efficacy parameter in this study was the percentage change in the whole scalp lesion score from Baseline (Week 0) to after the end of the study medication period. The primary comparison was between 5% tea tree oil and the placebo group patients.

The score for total area of involvement, total severity and whole scalp lesion (total area of involvement x total severity score) at Week 0 was summarised for all patients enrolled, by treatment group and overall.

Patient self assessment of scalp scaling, itching and greasiness on a 100 mm visual analogue scale (0=none and 100=worst ever) at Week 0 was summarised for all patients enrolled, by treatment group and overall.

Primary Efficacy Analysis

The primary efficacy variable was the mean percentage change in the whole scalp lesion score, from Week 0 (Baseline), to the patient's last assessment (Endpoint).

The percentage change from Week 0 in the whole scalp

lesions score, in addition to the actual score at Weeks 0, 2, 4 and at Endpoint, was summarised for both the Intention-to-Treat population and the efficacy evaluable population.

The percentage change from Week 0 to Endpoint in the group of patients treated with 5% tea tree oil was compared with the placebo group using Analysis of Variance. A 95% confidence interval for difference in mean percentage change, between the two treatment groups, was presented.

Secondary Efficacy Analyses

The total area of involvement score, and the total severity score were summarised (actual values and percentage change from Week 0) in an identical manner to that described above for the whole scalp lesions score. The percentage change from Week 0 to Endpoint was compared between treatment groups, also using the same methodology described in the previous section.

Patient Self Assessment

The primary tolerability measure was the change in each of the three components of the patient's self assessment (scaling, itching, and greasiness of scalp), from Week 0 (Baseline), to the patient's last assessment (Endpoint).

The actual scores at Weeks 0, 2, 4 and at Endpoint and the change from Week 0 for each of the three components of the patient's self assessment (scaling, itching and greasiness of scalp) at

Weeks 2, 4 and at Endpoint were summarised. The change from Baseline at Endpoint was compared between treatment groups using a two-sampled t-test / ANOVA since the data satisfies the underlying assumptions for this parametric test.

RESULTS

Primary Efficacy

Table 1 presents the primary efficacy results based on the Intention-to-Treat population, by treatment group. The results of Table 1 are also shown in FIG. 1.

The mean percentage decrease from Baseline to Endpoint in whole Scalp Lesion Score was 41.17% in the 5% tea tree oil treatment group compared to 11.16% for the placebo group.

There was a high statistically significant mean difference between 5% tea tree oil and the placebo treatment group (-30.01%, p-value <0.001). The 95% confidence interval, comparing 5% tea tree oil with placebo was -44.15% to -15.87%. This does not include 0, which enforces the conclusion drawn from the p-value regarding the statistically significant mean difference.

Results for the primary efficacy parameter based on the efficacy evaluable population are presented in Table 2.

For this population the mean percentage decrease from Baseline to Week 4 in Whole Scalp Lesion Score was 41.7% in the 5% tea tree oil treatment group, compared to 10.5% in the placebo

group at the Week 4 visit.

There was a statistically significant mean difference between 5% tea tree oil and the placebo treatment group (-31.17, p-value <0.001). The 95% confidence interval of this mean difference [-45.37, -16.98] does not include 0, which enforces the conclusion drawn from the p-value regarding the statistically significant mean difference.

Secondary Efficacy

Tables 3 and 4 present the secondary efficacy results based on the Intention-to-Treat population, by treatment group.

The mean percentage decrease from Baseline to Endpoint in Total Area of Involvement Score was 28.30% in the 5% tea tree oil group compared to 12.52% in the placebo group at the Endpoint visit.

The mean percentage decrease from Baseline to Endpoint in Total Severity Score was 23.35% in the 5% tea tree oil group compared to a mean percentage decrease of 2.84% in the placebo group, at the Endpoint visit.

For the percentage change in both the Total Area of Involvement Score and Total Severity Score, there were statistically significant differences between 5% tea tree oil and placebo groups (p-values <0.001). The 95% confidence intervals of the respective mean differences, comparing TTO with placebo, (Total Area of

Involvement [-24.21, -7.36] and Total Severity [-32.25, -8.78]) do not include 0, which enforces the conclusions drawn from the p-values suggesting a statistically significant mean difference.

Results for the secondary efficacy parameters based on the efficacy evaluable population are presented in Tables 5 and 6.

For this population the mean percentage decrease from Baseline to Endpoint in Total Area of Involvement Score was 28.4% in the 5% tea tree oil group compared to 12.1% in the placebo group, at Week 4.

For the efficacy evaluable population, the mean percentage decrease from Baseline to Endpoint in Total Severity Score was 23.4% in the 5% tea tree oil group compared to 2.5% in the placebo group, at Week 4.

For the percentage change in both the Total Area of Involvement Score and Total Severity Score, there were statistically significant differences between 5% tea tree oil and placebo groups (p-values <0.001). The 95% confidence intervals of the respective mean differences, comparing TTO with placebo, (Total Area of Involvement [-24.88, -7.80] and Total Severity [-32.75, -9.09]) do not include 0, which enforces the conclusions drawn from the p-values suggesting a statistically significant mean difference.

Patient Self Assessment

Table 7 presents the secondary efficacy results based on

the Intention-to-Treat population, by treatment group.

The mean decrease from Baseline to Endpoint in Scaling of Scalp was 25.6 in the 5% tea tree oil group. This compares to a mean decrease of 16.9 in the placebo group at the Endpoint visit. This mean difference, between 5% tea tree oil and placebo groups, was statistically significant (p-value: 0.033) at the 5% level of significance.

The mean decrease from Baseline to Endpoint in itching of Scalp was 23.0 in the 5% tea tree oil group. This compares to a mean decrease of 12.1 in the placebo group at the Endpoint visit. This mean difference, between 5% tea tree oil and placebo groups, was statistically significant at the 5% level of significance (p-value: 0.015).

The mean decrease from Baseline to Endpoint in Greasiness of Scalp was 25.9 in the 5% tea tree oil group. This compares to a mean decrease of 8.2 in the placebo group at the Endpoint visit. This mean difference, between 5% tea tree oil and placebo groups, was statistically significant at the 1% level of significance (p-value: <0.001).

Results for the secondary efficacy parameters based on the efficacy evaluable population are presented in Table 8.

For this population the mean decrease from Baseline to Week 4 in Scaling of Scalp was 25.4 in the 5% tea tree oil group.

This compares to a mean decrease of 17.4 in the placebo group at the Week 4 visit. This mean difference, between 5% tea tree oil and placebo groups, was statistically significant at the 5% level of significance (p-value: 0.048).

For the efficacy evaluable population, the mean decrease from Baseline to Week 4 in itching of Scalp was 23.1 in the 5% tea tree oil group. This compares to a mean decrease of 13.0 in the placebo group at the Week 4 visit. This mean difference, between 5% tea tree oil and placebo groups, was statistically significant (p-value: 0.020) at the 5% level of significance.

The mean decrease from Baseline to Week 4 in Greasiness of Scalp was 26.5 in the 5% tea tree oil group. This compares to a mean decrease of 8.4 in the placebo group at the Week 4 visit. This mean difference, between 5% tea tree oil and placebo groups, was statistically significant (p-value: <0.001) at the 1% level of significance.

CONCLUSIONS ON COMPARISON BETWEEN EXAMPLE 1 AND EXAMPLE 2

It was found when evaluating the formulation of 1.0%, 2.5% and 5.0% tea tree oil that total surfactant concentration was calculated to be 20.5%, 24.5% and 29.5%.

Clearly the shampoo with 1.0% tea tree oil and 20.5% total surfactant concentration was representative of prior art

shampoos as discussed above and was found to be unsatisfactory in use and did not demonstrate effectiveness when compared to placebo. Also the shampoos with (i) 2.5% tea tree oil and 24.5% surfactant concentration and (ii) 5.0% tea tree oil and 29.5% surfactant concentration were found to be unsatisfactory in use and did not demonstrate effectiveness in use when compared to placebo. Clearly all shampoos failed in the first clinical trial referred to in Example 1 because of excessive levels of surfactant, which bound the tea tree oil in a matrix of the shampoo and did not allow the tea tree oil to reach the scalp. This is in marked contrast to the 5.0% tea tree oil formulation used in Example 2 which demonstrated a marked effectiveness in use when compared to placebo. This formulation had a total surfactant solids concentration of 13.4% which did not bind the tea tree oil and thus substantially all of the tea tree oil was able to access the scalp.

Page(s) 39-140 are claims pages
They appear after the table listings

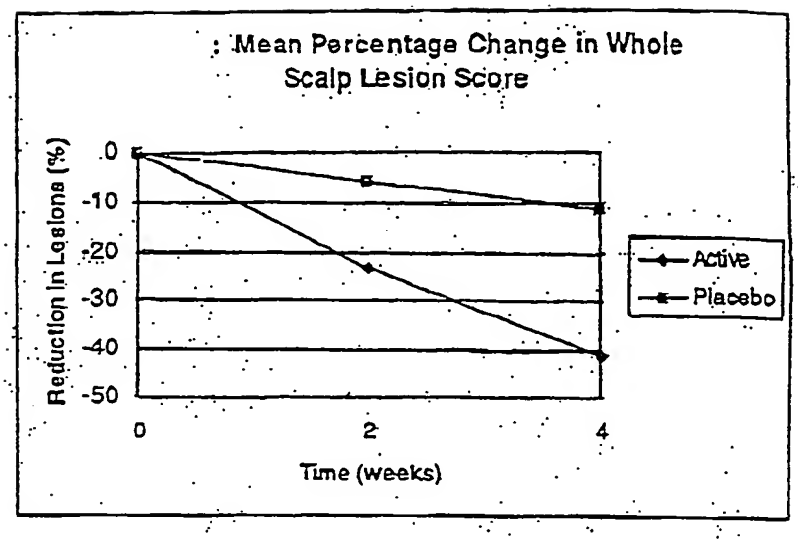
: Mean Percentage Change in Whole Scalp Lesion Score
Reduction in Lesions (%)
0
-10
-20
-30
-40
-50
0
2
4
Time (weeks)
Active
Placebo

FIG. 1

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Table 1
Percentage Change in Whole Scalp Lesion Score
Intention-to-Treat Population

Visit	Statistic	<-Treatment Group @-> TTO	PLACEBO	Mean Difference *	95% CI **	P-value @@
Week 2	N	63	62			
	Mean	-23.25	-5.86			
	SD	34.34	39.50			
	Median	-25.00	-5.77			
	Min	-84.6	-81.8			
	Max	69.7	120.0			
Week 4	N	63	62			
	Mean	-41.17	-11.16			
	SD	35.68	43.85			
	Median	-47.50	-13.25			
	Min	-100.0	-100.0			
	Max	52.7	113.3			
Endpoint	N	63	62			
	Mean	-41.17	-11.16	-30.01	(-44.15,-15.87)	<0.001
	SD	35.68	43.85			
	Median	-47.50	-13.25			
	Min	-100.0	-100.0			
	Max	52.7	113.3			

@ TTO = 5% Tea Tree Oil.
@@ p-value from Analysis of Variance, comparing treatment groups at Endpoint.
* Difference in Percent Mean Change from baseline at Endpoint, between TTO and Placebo
** 95% Confidence Interval of the respective Mean Difference.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Total Scalp Lesion Score = Total area of involvement x Total severity score.
: Endpoint = Last visit attended.

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Table 2
Percentage Change in Total Area of Involvement Score
Intention-to-Treat Population

Visit	Statistic	<-Treatment Group @-> TTO	PLACEBO	Mean Difference *	95% CI **	P-value @@
Week 2	N	63	62			
	Mean	-15.79	-7.65			
	SD	20.80	20.72			
	Median	-18.18	-6.46			
	Min	-69.2	-58.3			
	Max	28.6	36.4			
Week 4	N	63	62			
	Mean	-28.30	-12.52			
	SD	21.89	25.59			
	Median	-30.00	-7.69			
	Min	-73.3	-64.3			
	Max	27.3	45.5			
Endpoint	N	63	62			
	Mean	-28.30	-12.52	-15.78	(-24.21, -7.36)	<0.001
	SD	21.89	25.59			
	Median	-30.00	-7.69			
	Min	-73.3	-64.3			
	Max	27.3	45.5			

@ TTO = 5% Tea Tree Oil.
@@ p-value from Analysis of Variance, comparing treatment groups at Endpoint.
* Difference in Percent Mean Change from baseline at Endpoint, between TTO and Placebo
** 95% Confidence Interval of the respective Mean Difference.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Endpoint = Last visit attended.

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Table 3
Percentage Change in Total Severity Score
Intention-to-Treat Population

Visit	Statistic	<-Treatment Group @-> TTO	PLACEBO	Mean Difference *	95% CI **	P-value @@
Week 2	N	63	62			
	Mean	-12.29	-0.98			
	SD	25.34	28.99			
	Median	-14.29	0.00			
	Min	-60.0	-60.0			
	Max	66.7	83.3			
Week 4	N	63	62			
	Mean	-23.35	-2.84			
	SD	31.47	34.76			
	Median	-28.57	0.00			
	Min	-100.0	-100.0			
	Max	66.7	100.0			
Endpoint	N	63	62			
	Mean	-23.35	-2.84	-20.51	(-32.25, -8.78)	0.001
	SD	31.47	34.76			
	Median	-28.57	0.00			
	Min	-100.0	-100.0			
	Max	66.7	100.0			

@ TTO = 5% Tea Tree Oil.
@@ p-value from Analysis of Variance, comparing treatment groups at Endpoint.
* Difference in Percent Mean Change from baseline at Endpoint, between TTO and Placebo
** 95% Confidence Interval of the respective Mean Difference.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Endpoint = Last visit attended.

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Table 4
Percentage Change in Whole Scalp Lesion Score
Efficacy Evaluable Population

Visit	Statistic	<-Treatment Group @-> TTO	PLACEBO	Mean Difference*	95% CI**	P-value @@
Week 2	N	60	60			
	Mean	-23.23	-5.99			
	SD	35.20	40.10			
	Median	-24.04	-5.77			
	Min	-84.6	-81.8			
	Max	69.7	120.0			
Week 4	N	60	60			
	Mean	-41.69	-10.52	-31.17	(-45.37,-16.98)	<0.001
	SD	34.00	43.90			
	Median	-46.96	-13.25			
	Min	-100.0	-100.0			
	Max	52.7	113.3			

@ TTO = 5% Tea Tree Oil.
@@ p-value from Analysis of Variance, comparing treatment groups at Week 4.
* Difference in Percent Mean Change from baseline at Endpoint, between TTO and Placebo
** 95% Confidence Interval of the respective Mean Difference.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Total Scalp Lesion Score = Total area of involvement x Total severity score.

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Table 5
Percentage Change in Total Area of Involvement Score
Efficacy Evaluable Population

Visit	Statistic	<-Treatment Group @-> TTO	PLACEBO	Mean Difference*	95% CI**	P-value @@
Week 2	N	60	60			
	Mean	-16.12	-7.66			
	SD	21.19	21.03			
	Median	-18.18	-6.46			
	Min	-69.2	-50.3			
	Max	20.6	36.4			
Week 4	N	60	60			
	Mean	-20.44	-12.10	-16.34	(-24.88, -7.80)	<0.001
	SD	21.88	25.23			
	Median	-30.00	-7.69			
	Min	-73.3	-64.3			
	Max	27.3	45.5			

@ TTO = 5% Tea Tree Oil.
@@ p-value from Analysis of Variance, comparing treatment groups at Week 4.
* Difference in Percent Mean Change from baseline at Endpoint, between TTO and Placebo
** 95% Confidence Interval of the respective Mean Difference.

Note: Change = Visit Value - Baseline (Week 0) Value.

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Table 6
Percentage Change in Total Severity Score
Efficacy Evaluable Population

Visit	Statistic	<-Treatment Group @-> TTO	PLACEBO	Mean Difference*	95% CI**	P-value @@
Week 2	N	60	60			
	Mean	-12.15	-1.10			
	SD	25.06	29.44			
	Median	-14.29	0.00			
	Min	-60.0	-60.0			
	Max	66.7	83.3			
Week 4	N	60	60			
	Mean	-23.43	-2.51	-20.92	(-32.75, -9.09)	0.001
	SD	30.00	35.22			
	Median	-28.57	0.00			
	Min	-100.0	-100.0			
	Max	66.7	100.0			

@ TTO = 5% Tea Tree Oil.
@@ p-value from Analysis of Variance, comparing treatment groups at Week 4.
* Difference in Percent Mean Change from baseline at Endpoint, between TTO and Placebo
** 95% Confidence Interval of the respective Mean Difference.

Note: Change = Visit Value - Baseline (Week 0) Value.

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Table 7
Change in Patient Self Assessment
Intention-to-Treat Population

SYMPTOM = SCALING OF SCALP

Visit	Statistic	<---Treatment Group @---> TTO	PLACEBO	P-Value *
Week 2	N	60	60	
	Mean	-17.9	-15.5	
	SD	21.14	25.16	
	Median	-18.0	-8.0	
	Min	-72	-90	
	Max	26	39	
Week 4	N	60	61	
	Mean	-25.6	-16.9	
	SD	21.91	29.08	
	Median	-26.0	-13.0	
	Min	-79	-90	
	Max	35	41	
Endpoint	N	60	61	
	Mean	-25.6	-16.9	0.066
	SD	21.91	29.08	
	Median	-26.0	-13.0	
	Min	-79	-90	
	Max	35	41	

@ TTO = 5% Tea Tree Oil.
* p-value from Analysis of Variance, comparing treatment groups at Endpoint.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Endpoint = Last visit attended.

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Table 7 (continued)
Change in Patient Self Assessment
Intention-to-Treat Population

SYMPTOM = ITCHING (PRURITUS) OF SCALP

Visit	Statistic	<---Treatment Group @---> TTO	PLACEBO	p-Value
Week 2	N	60	60	
	Mean	-16.1	-8.5	
	SD	19.93	25.10	
	Median	-15.0	-7.5	
	Min	-57	-59	
	Max	29	57	
Week 4	N	59	61	
	Mean	-23.0	-12.1	
	SD	21.20	30.84	
	Median	-26.0	-7.0	
	Min	-69	-88	
	Max	40	55	
Endpoint	N	60	61	
	Mean	-22.6	-12.1	0.031
	SD	21.24	30.84	
	Median	-26.0	-7.0	
	Min	-69	-88	
	Max	40	55	

@ TTO = 5% Tea Tree Oil.
* p-value from Analysis of Variance, comparing treatment groups at Endpoint.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Endpoint = last visit attended.

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Protocol TTOILDAN02

Table 7 (continued)
Change in Patient Self Assessment
Intention-to-Treat Population

SYMPTOM = GREASINESS OF SCALP

Visit	Statistic	<---Treatment Group @---> TTO	PLACEBO	P-Value *
Week 2	N	60	60	
	Mean	-19.4	-8.6	
	SD	22.49	23.36	
	Median	-17.0	-3.5	
	Min	-67	-72	
	Max	33	56	
Week 4	N	60	61	
	Mean	-25.9	-8.2	
	SD	28.07	28.92	
	Median	-26.0	-2.0	
	Min	-92	-87	
	Max	45	83	
Endpoint	N	60	61	
	Mean	-25.9	-8.2	0.001
	SD	28.07	28.92	
	Median	-26.0	-2.0	
	Min	-92	-87	
	Max	45	83	

@ TTO = 5% Tea Tree Oil.
* p-value from Analysis of Variance, comparing treatment groups at Endpoint.

Note: Change = Visit Value - Baseline (Week 0) Value.
: Endpoint = Last visit attended.

Table 8
Change in Patient Self-Assessment
Efficacy Evaluable Population

SYMPTOM = SCALING OF SCALP

Visit	Statistic	<---Treatment Group @---> TTO	PLACEBO	P-value *
Week 2	N	50	59	
	Mean	-18.3	-15.6	
	SD	21.24	25.34	
	Median	-18.0	-9.0	
	Min	-72	-90	
	Max	26	39	
Week 4	N	58	60	
	Mean	-25.4	-17.4	0.096
	SD	22.26	29.08	
	Median	-25.5	-14.0	
	Min	-79	-90	
	Max	35	41	

@ TTO = 5% Tea Tree Oil.
* p-value from Analysis of Variance, comparing treatment groups at Week 4.

Note: Change = Visit Value - Baseline (Week 0) Value.

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Table 8 (continued)
Change in Patient Self Assessment
Efficacy Evaluable Population

SYMPTOM = ITCHING (PRURITUS) OF SCALP

Visit	Statistic	<---Treatment Group @---> TTO	PLACEBO	P-value *
Week 2	N	58	59	
	Mean	-16.0	-9.6	
	SD	20.15	23.79	
	Median	-15.0	-8.0	
	Min	-57	-59	
	Max	29	55	
Week 4	N	57	60	
	Mean	-23.1	-13.0	0.040
	SD	21.34	30.34	
	Median	-26.0	-7.5	
	Min	-69	-88	
	Max	40	55	

@ TTO = 5% Tea Tree Oil.
* p-value from Analysis of Variance, comparing treatment groups at Week 4.

Note: Change = Visit Value - Baseline (Week 0) Value.

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Table 8 (continued)
Change in Patient Self Assessment
Efficacy Evaluable Population

SYMPTOM : GREASINESS OF SCALP

Visit	Statistic	<---Treatment Group @---> TTO	PLACEBO	P-value *
Week 2	N	58	59	
	Mean	-19.7	-8.5	
	SD	22.72	23.55	
	Median	-17.0	-3.0	
	Min	-67	-72	
	Max	33	56	
Week 4	N	58	60	
	Mean	-26.5	-8.4	0.001
	SD	28.05	29.15	
	Median	-26.0	-2.0	
	Min	-92	-87	
	Max	45	83	

@ TTO = 5% Tea Tree Oil.
* p-value from Analysis of Variance, comparing treatment groups at Week 4.

Note: Change = Visit Value - Baseline (Week 0) Value.

CLAIMS

1. A formulation containing 0.25-15.0% w/v tea tree oil and 1-15% w/v of a surfactant.

2. A formulation as claimed in claim 1 including 0.1-2.0% w/v of other topically active components.

3. A formulation as claimed in claim 2 wherein the topically active components are selected from zinc pyrithione, sulphur, selenium sulphide, coal tar, salicylic acid and piroctone olathine.

4. A formulation as claimed in any preceding claim wherein the surfactant is an anionic surfactant.

5. A formulation as claimed in any preceding claim wherein the anionic surfactant is selected from sodium lauryl sulfate, sodium lauryl ether sulfate or ammonium lauryl sulfate.

6. A formulation as claimed in any preceding claim containing 0.5-5.0% w/v tea tree oil.

7. A formulation as claimed in any preceding claim containing from 0.5-2.0% of tea tree oil.

8. A formulation as claimed in any preceding claim wherein the maximum amount of surfactant is 13.4% w/v.

9. A formulation as claimed in any preceding claim when used as a mouthwash, cream, or shampoo.

10. A formulation as claimed in claim 9 when used as a shampoo.

11. A formulation as claimed in any one of claims 1-8 when used as an anti-dandruff preparation.

12. A method of increasing the efficiency of active of use of tea tree oil as a therapeutic which includes the step of providing a formulation which provides a maximum concentration of unbound or free tea tree oil in a surfactant wherein the level of surfactant is maintained at a maximum concentration of 15% w/v.

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